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A selective hydration of nitriles catalysed by a $Pd(OAc)_2$-based system in water

Daniel D. Sanz Sharley[a*] and Jonathan M. J. Williams[a]

[a] *Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, UK*

*Corresponding author. Tel.: +447708611108; e-mail: D.D.Sanz.Sharley@bath.ac.uk

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ABSTRACT

In situ formation of a [$Pd(OAc)_2$bipy] (bipy = 2,2'-bipyridyl) complex in water selectively catalyses the hydration of a wide range of organonitriles at 70 °C. Catalyst loadings of 5 mol% afford primary amide products in excellent yields in the absence of hydration-promoting additives such as oximes and hydroxylamines.

The formation of amides is a key transformation in organic chemistry given the prevalence of the functionality in pharmaceuticals, fabrics, lubricants, fertilisers and plastics.[1] As a result of their importance and the need for cleaner protocols, the last decade has seen the emergence of a wide range of amidation methods with increased atom efficiency.[2] One of the most attractive methods for the preparation of primary amides, in both industry and academia, is the hydration of nitriles.[1,3] However, traditional methods using strong acids and bases suffer several drawbacks, including the formation of carboxylic acids through over-hydrolysis of the desired amide products, as well as low functional group tolerance.[4]

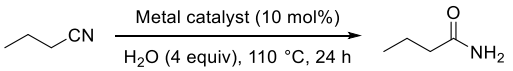
In the search for a more attractive and applicable method for hydrating nitriles, the use of acetaldoxime as an additive has been investigated.[5] However, the need for at least stoichiometric amounts of the oxime and the risk of a competing hydration reaction involving the liberated nitrile is less than ideal. Other research has focused on employing hydroxylamines to promote the hydration reaction;[6] however, similar to the use of oximes, H_2O^{18}-labelling experiments confirmed that it is the hydroxylamine that participates in the reaction and not water.[1]

In contrast, the most attractive approach for hydrating nitriles involves the use of water without the need for oxime/hydroxylamine-type additives. As such, recent work in the area has focused on the development of suitable catalysts that enable such a transformation to occur. These catalysts include Ru,[7] Rh,[8] Ag,[9] and Mn[10] complexes, as well as metal nanoparticles.[11] However, despite improvements in the efficiency of the hydration reaction, these approaches often require very expensive catalysts, prior synthesis of the active catalyst and/or heating at reflux.

Initially, we screened a wide range of commercially available metal complexes using the hydration of butyronitrile as a model reaction, in order to find a more attractive catalytic system. Employing a catalyst loading of 10 mol% and 4 equivalents of water it was found that palladium complexes gave the highest conversions (Table 1). Among these, palladium acetate proved to be the most efficient catalyst. In contrast, cheaper, first row metal complexes resulted in no conversion into the primary amide product.

The use of palladium-based catalysts for the hydration of nitriles has previously been explored. Among the heterogeneous examples,[12] palladium nanoparticles, in combination with other compounds such as metal oxides, have received a lot of attention.[13] Other methods utilise homogeneous catalysts,[14] including $Pd(OAc)_2$-based complexes.[13a,15] However, these

Table 1
Initial metal catalyst screen[a]



Entry	Metal Complex	Conversion (%)[b]
1	-	0
2	$Pd(OAc)_2$	73
3	$Pd(NO_3)_2 \cdot xH_2O$	55
4	$PdCl_2$	13
5	$PdCl_2(MeCN)_2$	15
6	$PdCl_2(PhCN)_2$	7
7	$Pd(acac)_2$	0

[a] 25 catalysts screened - see ESI, Table S1 for full details.

[b] Conversion determined by ^{1}H NMR analysis.

methods require an additional Lewis acid co-catalyst[15a] or complex co-ligands,[13a] whilst other approaches also utilising $Pd(OAc)_2$ only operate in the presence of an oxime, as described earlier.[15b,15c] As well as this, many protocols only exhibit a very limited substrate scope.

In the course of our own studies, we subsequently showed that the use of water as a solvent (with a reaction concentration of 1 M) instead of only 4 equivalents afforded a cleaner reaction and aided stirring. Due to the cost of $Pd(OAc)_2$ it was necessary to reduce the catalyst loading; although doing so under the present reaction conditions resulted in decreased conversion into butyronitrile. It was noticed, however, that a black precipitate was forming, likely due to decomposition of the catalyst to palladium black, even with reduced temperatures of 80 °C.

It was clear a coordinating ligand needed to be introduced into the reaction mixture in order to stabilise the catalyst, similar to previous studies. Oberhauser and co-workers showed $Pd(OAc)_2$ could be solubilised in water using a poly(ethyleneglycol) monomethylether functionalised bipy ligand.[13a] Using this concept, we wanted to investigate whether a non-functionalised bipy unit could perform the same role in our system. Pleasingly, the much cheaper and readily available bipy ligand was able to solubilise the palladium catalyst *in situ* and increase conversions at 80 °C. Investigations into the ratio of bipy to $Pd(OAc)_2$ revealed a 1:1 stoichiometry to be optimal; employing 5 mol% of each led to quantitative conversion. However, a decrease in reaction temperature to 60 °C led to reduced conversion into butyramide (Table 2, entry 2).

At this point, we decided to investigate whether altering the electronic properties of the bipy moiety influenced the hydration reaction (Table 2, entries 2-7). Introducing electron withdrawing and electron donating groups to the 4-position of bipy made little difference to the efficiency of the reaction, although preforming the active catalyst prior to addition of the nitrile led to slightly increased conversion (Table 2, entry 3). Other common mono-, bi- and tridentate nitrogen ligands were also investigated (Table 2, entries 8-13); however, no considerable increase in conversion was seen and in some cases the ligand inhibited the hydration reaction (Table 2, entries 11 and 12). In addition, the use of phosphines and more unusual bidentate nitrogen ligands resulted in poor conversions.

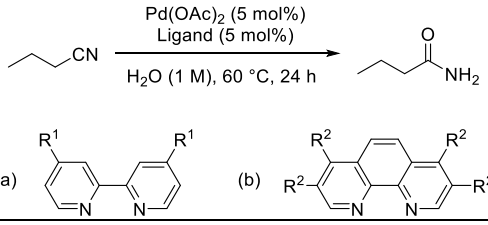
As a result, these findings and the ready availability of bipy led us to continue our study using this ligand in combination with $Pd(OAc)_2$. An elevated temperature of 70 °C allowed higher conversions to be achieved and pleasingly, the reaction could be driven to quantitative conversion when increased water (0.5 M) was employed. However, catalyst loadings lower than 5 mol% did not yield full conversion. It should also be noted that preformation of the catalyst had no beneficial effect at this temperature. Meanwhile, employing increased amounts of water in the reaction at the lower temperature of 60 °C afforded decreased conversions, even when the catalyst was preformed (see ESI for further details).

Subsequently, less expensive first row metal acetate complexes, namely $Ni(OAc)_2{\cdot}4H_2O$ and $Cu(OAc)_2$, were investigated as catalysts for the reaction under these new conditions. However, no conversion was observed either in the presence or absence of bipy. In addition, it is interesting to note that using the slightly cheaper $PdCl_2$ as the catalyst in the presence of bipy resulted in only 5% conversion into butyramide, compared with 33% conversion without the ligand present.

The fully optimised methodology was then applied to a comprehensive range of nitriles (Table 3). During investigations into the substrate scope it was noticed that some substrates, particularly aromatic nitriles, were insoluble in water and therefore dioxane was used as a co-solvent in these cases. Aliphatic nitriles were transformed into their corresponding primary amide products in excellent yield (**1a**-**1f**), including the vinylic example **1c**. Pleasingly, primary amide **1d** was also afforded in excellent yield with no by-products observed from palladium insertion into the C-Br bond. Electron-withdrawing substituents in the *ortho*, *meta* and *para* positions of benzonitrile were well tolerated by the reaction conditions, including acetyl (**1p**), ester (**1q**), nitro (**1m**, **1n** and **1o**), halogenic (**1h**, **1k** and **1l**) and trifluoromethyl (**1i**) groups. Benzonitrile substrates containing electron-donating groups in the *meta* and *para* positions, such as methyl (**1t** and **1u**), methoxy (**1j**) and hydroxy (**1s**) moieties, were also converted into their primary amide products in good to excellent yield, although nitriles with donating *ortho*-substituents were transformed less efficiently. This is likely a result of both steric effects and electron donation into the nitrile carbon which reduces its electrophilicity.

Nitriles containing heteroaromatic groups such as examples **1z** and **1aa** also proved to be compatible with the methodology, although nitrogen-containing heteroaromatic nitriles gave low conversions when subjected to the protocol. We hypothesised that this was likely to be a result of the nitrogen competing with the nitrile for coordination to the palladium. This was strengthened by two studies in which the presence of pyrrole and pyridine in our model reaction was found to completely inhibit the formation of butyramide (Scheme 1). In addition, the use of one equivalent of acid in the hydration reaction involving 4-pyridinecarbonitrile, in order to protonate the competing nitrogen and thus block coordination to the palladium, afforded no conversion. However, increased steric bulk around the competing

Table 2
Ligand screen[a]

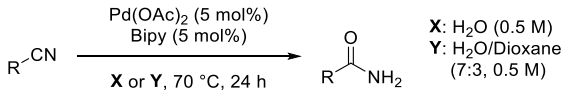


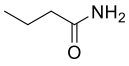
Entry	Ligand	Conversion (%)[b]
1	No Ligand	30
2	(a) R^1 = H	70
3	(a) R^1 = H (Catalyst preformed)	80
4	(a) R^1 = OMe	74
5	(a) R^1 = CO_2Me	76
6	(a) R^1 = Br	79
7	(a) R^1 = ^{t}Bu	77
8	(b) R^2 = H	78
9	(b) R^2 = Me	83
10	Terpyridine	70
11	Ethylenediamine	17
12	Imidazole	3
13	Pyridine	34

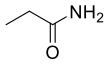
[a] 25 ligands screened - see ESI, Table S4 for full details.

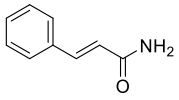
[b] Conversion determined by ^{1}H NMR analysis.

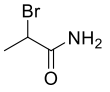
Table 3
Scope of the hydration of nitriles[a,b]

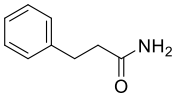


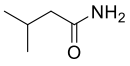

1a X: 100 (97)

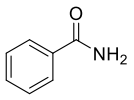

1b X: 91 (88)

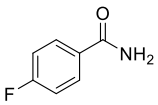

1c X: 77
Y: 96 (93)

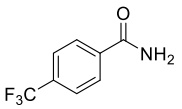

1d X: 87 (85)

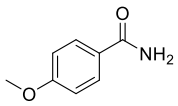

1e X: 97 (91)

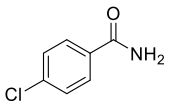

1f X: 80 (75)

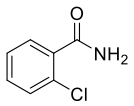

1g X: 100 (97)

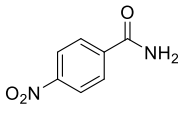

1h X: 91 (90)

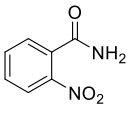

1i X: 96 (95)

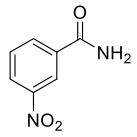

1j X: 80 (76)
Y: 83

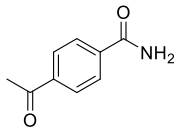

1k X: 76 (71)
Y: 100 (98)

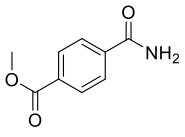

1l X: 41
Y: 73 (71)

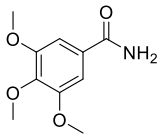

1m X: 76
Y: 100 (98)

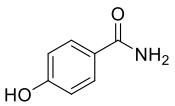

1n X: 86
Y: 100 (98)

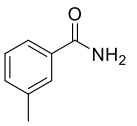

1o X: 84
Y: 100 (98)

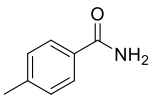

1p X: 100 (98)
Y: 100

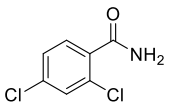

1q X: 80
Y: 100 (95)

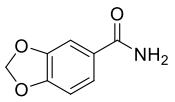

1r X: 19
Y: 100 (96)

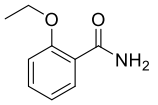

1s X: 93 (85)
Y: 94

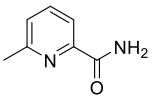

1t X: 82 (77)

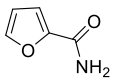

1u X: 69
Y: 100 (95)

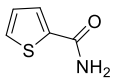

1v X: 47
Y: 88 (84)


1w X: 97 (93)
Y: 97


1x Y: 100 (98)[c]


1y X: 80
Y: 88 (84)

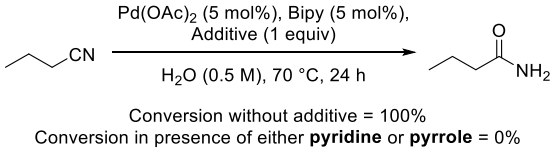

1z X: 100 (96)


1aa X: 100 (98)

[a] Conversion determined by ^{1}H NMR analysis, isolated yields shown in parentheses.

[b] See ESI, Table S11 for less successful substrates.

[c] Reaction performed at 90 °C (68% conversion at 70 °C (**Y**)).



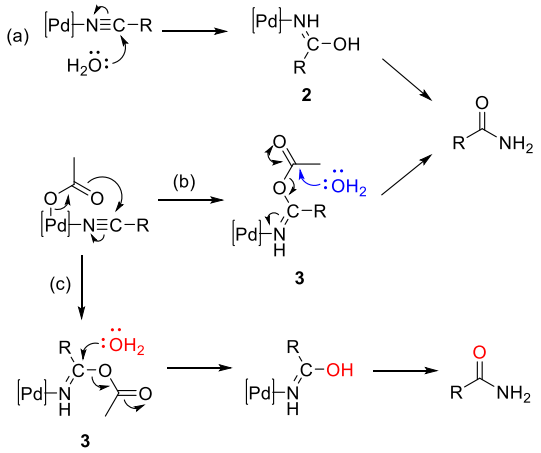
Scheme 1. Investigations into competing N-coordination.

nitrogen allowed efficient hydration of the nitrile (**1y**).

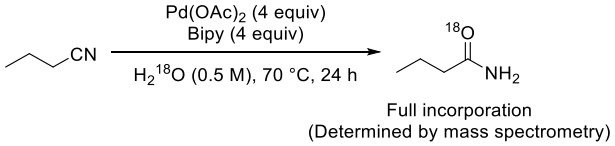
Although electron-donating groups in the *ortho* position hinder the efficiency of the hydration reaction, we showed that increased temperatures could be used to drive the reaction to quantitative conversion. This allowed us to synthesise ethenzamide (**1x**), a common analgesic and anti-inflammatory drug, in excellent yield, thus illustrating the pharmaceutical applicability of the methodology. In addition, the scalability of the methodology was also verified by performing the hydration of benzonitrile on a 40 mmol scale (94% isolated yield).

Finally, we hypothesised that the reaction mechanism could proceed through three plausible routes, all of which begin with coordination of the nitrile to the palladium centre (Scheme 2). This generally accepted mechanism increases the electrophilicity of the nitrile carbon, thus increasing its susceptibility to nucleophilic attack.[16] From here, one possible route involves direct attack by water followed by the rearrangement of iminolate species **2** to afford the desired amide (pathway (a)). Alternatively, the reaction may proceed *via* intermediate **3**, formed from the internal delivery of oxygen by the acetate ligand of the metal catalyst. Intermediate **3** can then undergo nucleophilic attack by water through either pathway (b) or pathway (c) *en route* to the primary amide product.

In order to elucidate information on the reaction mechanism, a $H_2{}^{18}O$ labelling study was performed (Scheme 3). Employing $H_2{}^{18}O$ and excess $Pd(OAc)_2$ in our model reaction, quantitative incorporation of the ^{18}O label was observed by mass spectrometry (see ESI). As a result of this, pathway (b) can be discounted from the plausible mechanisms.



Scheme 2. Plausible mechanisms for the $Pd(OAc)_2$-catalysed hydration of nitriles.



Scheme 3. Hydration of butyronitrile using $H_2{}^{18}O$.

Further mechanistic studies are to be performed in the future; however, the increased efficiency observed when employing $Pd(OAc)_2$ compared with $PdCl_2$ may suggest that the acetate ligands participate in the reaction mechanism.

In summary, we have reported a selective, relatively mild and fully optimised methodology for the hydration of organonitriles in water, without the use of hydration-promoting additives such as oximes and hydroxylamines. *In situ* formation of a [$Pd(OAc)_2$bipy] complex catalyses the transformation of a wide array of aliphatic and aromatic nitriles into their primary amide products in excellent yields. We believe our method successfully combines simplicity with synthetic utility.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at xx.

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